Title of research study: INdividualized ITI based on fviii(ATE) protection by VWF (INITIATE)

Investigators:

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This form is being reviewed with (check all that apply):

☐ An adult **(age 18 years and up)** who may become a study participant.

☐ The parent or legal guardian **(age 18 years and up)** of a minor under 18 years of age who may become a study participant. *Please note that "you" means your child because you are consenting for your child.*

Why am I being invited to take part in a research study?

We invite you to take part in a research study because you have congenital Hemophilia A, FVIII activity ≤2%, and a historical high-titer inhibitor. This consent document is for use in a research study that will involve research participants who may or may not have the capacity to consent to their participation. In this consent document, "you" refers to the research participant. If you are a parent or legal guardian, please remember that "you" refers to your child.

What should I know about a research study?

(Experimental Subject's Bill of Rights)

- Someone will explain this research study to you, including:
  - The nature and purpose of the research study.
  - The procedures to be followed.
  - Any drug or device to be used.
  - Any common or important discomforts and risks.
  - Any benefits you might expect.
  - Other procedures, drugs, or devices that might be helpful, and their risks and benefits compared to this study.
  - Medical treatment, if any, that is available for complications.
- Whether or not you take part is up to you.

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- You can choose without force, fraud, deceit, duress, coercion, or undue influence.
- You can choose not to take part.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- You can ask all the questions you want before you decide.
- If you agree to take part, you will be given a signed and dated copy of this document**.**
- If you agree to take part, you will be given a copy of this document.

If you decide to take part in this research study, you will be asked to sign this consent document before any study-related activities are performed. You will receive a copy of this signed consent document for your records.

Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team listed at the top of this form.

For non-emergency issues you can call the UCDMC Hospital Operator (916-734-2011), tell the Operator you are participating in a research study and you wish to talk to the hematologist on call. In the case of an emergency, dial 911 from any phone.

This research has been reviewed and approved by an Institutional Review Board ("IRB"). Information to help you understand research is on-line at http://www.research.ucdavis.edu/policiescompliance/irb-admin/.You may talk to a IRB staff member at (916) 703-9151, hs-irbadmin@ucdavis.edu, or 2921 Stockton Blvd, Suite 1400, Room 1429, Sacramento, CA 95817 for any of the following:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

Why is this research being done?

Many people being treated for severe Hemophilia A experience serious complications due to antibodies that form during treatment. Immune Tolerance Induction (ITI) therapy is a program of regular infusions over a prolonged period of time - from a few months to a few years - to remove these antibodies and improve overall treatment. This research will study the effectiveness of ITI, as well as the best ways to implement ITI to improve the treatment of people with severe Hemophilia A.

The rationale for this study is that an optimal regimen for ITI has not been identified, and patients with Hemophilia A and inhibitors have high rates of illness, mortality, and associated costs. We hope to learn if there are potential advantages of using a patient-specific laboratory test called batch-selection to decrease the time to success in Immune Tolerance Induction (ITI) for hemophilia A patients with inhibitors to FVIII.

Participants in this study will be randomized on a two-to-one basis between one of two study arms, matched lot selection (alternative treatment arm) and random lot selection (standard treatment arm,

current US clinical practice in ITI). The purpose of this study is to compare the time to achieve negative inhibitor (<0.6 BU) between matched lot selection to random lot selection.

OPTIONAL GENETIC RESEARCH:

There is an opportunity for us to comprehensively study certain aspects of inhibitors and the induction of immune tolerance through this study. This would require us to collect an additional 2 teaspoons of blood during your screening visit. This optional research will look at genetic risk factors and a person's response to immune tolerance induction and genetic testing to identify the causative factor VIII mutation.

If you agree to participate in the optional research, please initial here: _____

If you do NOT want to participate in the optional research, please initial here: _____

How long will the research last?

We expect that you will be in this research study for up to 36 months.

How many people will be studied?

We expect up to 6 people here will be in this research study out of 120 people in the entire study nationally.

What happens if I say yes, I want to be in this research?

Before any study procedures begin, you will be asked to sign this consent form. The study doctor will examine you and ask you questions to determine if you are eligible for the study. If blood samples were already collected prior to signing this consent form, then you may not need to have additional blood samples collected for the screening visit activities described below.

If you have had any prior ITI therapy, the prior ITI regimen must have been discontinued within 1 month of study enrollment unless there is clear evidence of ITI failure with no reduction in inhibitor titer over the past 2 months.

The screening visit should take place within 35 to 56 days of the baseline visit (a period of time known as the screening period). Blood samples for laboratory tests no more than 35 days before the baseline visit. The tests and assessments that you will have are shown in Table 1.You will have evaluations on a monthly basis until ITI is completed. Evaluations must be performed at the clinical site at least every 8 weeks. Clinical evaluations will be performed by telephone call 4 weeks after every in-person visit performed at the clinical site.

If at 6 months it is found that you still have inhibitors and you are in the standard treatment arm (random lot selection), you may be switched to the alternative treatment arm of the study.

Table 1. Assessments performed at each visit

Study visit	Duration or time point	Procedures
Screening period	Up to 56 or 35 days	• Sign the Informed Consent Form (up to 56 days) • Check whether the study is right for you (up to 56 days) • Check of your medical history (up to 35 days) • Questions about whether you have received any other medications or non-drug therapies (up to 35 days) • Clinical information will be collected (up to 35 days) • Receive the patient diary and training on its use (up to 35 days) • Quality of Life assessment (up to 35 days) • Laboratory evaluations (up to 35 days) • Weight and height measurement (up to 35 days) • We will determine the size of the study-specific refrigerator you will use and we will arrange for it to be sent to your home • Randomization to treatment arm
Immune Tolerance Induction treatment period visits and Follow-up after complete or partial success	• Day 0 (Baseline Visit in-person) • Week 2 (in- person) • Week 4 (in-person) • Every 4 weeks after week 4 (in-person or phone) • Every 8 weeks after complete or partial success (in-person or phone)	Some or all of the following may happen at your visit: • Check whether the study is right for you • Sign the Informed Consent Form (if a minor child participant turns 18 years old) • You will start Immune Tolerance Induction treatment • Review of patient diary and discussion of any bleeding episodes and their treatment • Check of your medical history • Questions about whether you have received any other medications or non-drug therapies • Quality of Life assessment (as applicable) • Laboratory evaluations • Weight and height measurement as applicable • Assessment of your compliance with your ITI dosing regimen • Check your supply of Wilate® • Collect empty vials and boxes of Wilate®

The assessments described in Table 1 are described below.

The following clinical information will be collected during the screening period:

a) Hemophilia history

b) Current and prior hemophilia treatment information

c) Blood tests

The following information will be collected during your follow-up visits:

- Concomitant medications
- Medical history
- Bleeding history
- Quality of life (as applicable)
- ITI-related adverse events and serious adverse events
- Height/weight (as indicated in the schedule of events)
- Diary information

Questions about your health and medications

The study doctor will ask if you have experienced any changes in your health, or any new symptoms since your last visit. They will also ask if you have taken any new medications (including prescription, over-the-counter, or other medications) since your last visit.

Laboratory evaluations

Blood samples will be collected to conduct blood tests. Approximately 21 mL (about 4 teaspoons) of blood will be collected during the screening visit. If you opt into the optional genetic testing, an additional 5.5 mL (about 1 teaspoon) will be collected.

During the Immune Tolerance Induction (ITI) and Follow-Up portion, approximately 6mL (about 2 teaspoons) will be collected each time a laboratory evaluation is performed.

Blood tests will be done based on response to ITI.

Review of patient diary

Throughout study participation, you will be asked to fill out a patient diary. You will be given the diary during the screening visit, and it will be reviewed at each subsequent study center visit. You will be shown how to use the diary, in which you will need to record the following information:

- Information about Wilate® infusions
- Details of bleeding episodes and response to treatment, including the location, type, and severity of the bleed; the date and time of its onset and resolution; the date and time of each infusion/injection required to stop the bleed
- Whether you experienced any untoward events.

The diary will be collected from you at every in-person visit and a new diary will be dispensed.

Randomization

The treatment you get will be chosen by chance, like flipping a coin. Neither you nor the study doctor will choose what treatment you get. You will have a two to one (2:1) chance of being given the alternative treatment over the standard treatment. Neither you nor the study doctor will know which treatment you are getting.

Wilate® will be stored at your house in the myCubixx refrigerator or in your own refrigerator. The MyCubixx refrigerator will be provided by ASD Healthcare.

The research team will notify ASD Healthcare of your enrollment into the study in a manner that does not include your name, address, or other identifying information. ASD Healthcare will arrange, through a third party affiliate, for a myCubixx device to be delivered to and installed at your house. The research team will assist ASD Healthcare in arranging for the delivery of the myCubixx device to your house upon enrollment and the return of the myCubixx device upon termination of the study.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible to:

- Report to the study clinic for all scheduled visits, lab draws, and other visits as requested by the study staff.
- Comply with all instructions provided by the doctor at the study site.
- Follow instructions for keeping an accurate study diary.
- Bring all empty vials and boxes of Wilate® to all your visits.
- Report any changes in your symptoms or in how you feel. Tell the doctor if you have seen another doctor, had a visit to the Emergency Room, or if you were admitted to the hospital.

It is important that you immediately report any new symptoms or worsening of symptoms that you have to the study staff so they may follow you appropriately.

If you take any of the following products, you are required to report them to your study doctor or study staff:

- Medications that are prescribed by any doctor.
- Over-the-counter medications.
- Vitamins and dietary supplements.

Any medications you take during the study will be recorded by the study staff to ensure your safety and well-being. You should call the study doctor before taking any new medication.

You must inform the Investigator if you anticipate any changes to your routine medication(s). Usage of clotting factors (date, dosage, reason) will be recorded in the study diaries.

What happens if I do not want to be in this research?

You may decide not to take part in the research and it will not be held against you. Participation in this study is voluntary. You are free to refuse to participate or stop taking part in the study at any time

without any penalty or loss of benefits to which you are otherwise entitled. Your decision to participate or not participate will in no way affect your current or future treatment. You will be given all the needed time and opportunity to ask questions about the details of this study and to decide if you want to participate.

There are options for you other than this research study including:

- Not participating in this study.
- Getting standard treatment for your condition without being in a study.
- Getting a different experimental treatment or taking part in another study.

What happens if I say yes, but I change my mind later?

You can leave the research at any time and it will not be held against you. Your participation can be stopped safely. You will be asked to return to the study center for a final safety evaluation. Please consult with your study doctor to discuss the safest way to withdraw from the study if you wish to leave early.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

Is there any way being in this study could be bad for me?

Your study doctor /study staff will routinely follow-up with you to ensure the risks and/or benefits are monitored.

Allergic reactions: Any medicine which is prepared from human blood and which is injected into a vein (administered intravenously), such as Wilate®, can cause allergic reactions. Please pay attention to early signs of allergic reactions (hypersensitivity), such as hives, skin rash, tightness of the chest, wheezing, low blood pressure, or anaphylaxis (when any or all of the above symptoms develop rapidly and are intense). If these symptoms occur, stop the injection immediately and contact the study doctor. These reactions have been found to be uncommon, i.e., they may affect up to 1 in 100 people.

Transmission of infection: When medicines are made from human blood, certain measures are put in place to prevent infections from being passed on to patients. These measures include careful selection of blood and plasma donors to make sure donors at risk of carrying infections are ex-cluded, the testing of each donation and pools of plasma for signs of infections, and manufacturing steps that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood are administered, the possibility of passing on infection cannot be totally ex-cluded. This also applies to any unknown or emerging viruses or other types of infections. The measures taken are considered effective for enveloped viruses, such as human immunodeficiency virus (HIV), hepatitis B virus, and hepatitis C virus, and for the non-enveloped hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

Wilate® may increase the risk of thromboembolic (clotting) events.

Blood Draw Risks: Using a needle to remove blood from a vein is called "a blood draw." It may be necessary to try more than once. A new needle will be used for each blood draw. Blood samples will be taken throughout the study. You might feel pain or be light-headed from this. You may experience some temporary discomfort, bleeding, bruising, swelling or rarely, infection, at the site of a needle stick.

A total of about 2 teaspoons of blood will be collected at each clinic visit.

Randomization: Patients will be assigned to a treatment program by chance, and the treatment a patient receives may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.

There is also a minimal risk of loss of confidentiality.

In addition to these risks, this research may hurt you in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.

If you decide to participate in the optional genetic research:

There is a small risk of health insurance discrimination based on genetic testing; however, per the Genetic Information Nondiscrimination Act of 2008 (GINA), group and individual health insurers may not use your genetic information to set insurance eligibility, premiums, or contribution amounts, nor can they request or require that you take a genetic test. In addition, employers with 15 or more employees may not use your genetic information to make decisions regarding hiring, firing, job assignments, or promotions, nor can they request, require, or purchase your genetic information. In Ohio, there is a similar state law that also provides some protection for private health insurance plans. GINA does not protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance.

Will being in this study help me in any way?

If you decide to take part in this research study, there is no guarantee there will be any benefit to you. Your condition may become worse or may improve. There may or may not be direct benefit for you now, but information from this study may benefit other people now or in the future. The results of this study may help us learn if there are potential advantages of utilizing a patient-specific laboratory test called batch-selection to decrease the time to success in Immune Tolerance Induction (ITI) for hemophilia A patients with inhibitors to FVIII. This research may give rise to new or better treatments.

What happens to the information collected for the research?

Efforts will be made to limit use or disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information include the IRB and other University of California representatives responsible for the management or oversight of this study.

Biospecimens (such as blood, tissue, or saliva) collected from you for this study and/or information obtained from your biospecimens may be used in this research or other research, and shared with other organizations. You will not share in any commercial value or profit derived from the use of your biospecimens and/or information obtained from them."

If you receive the MyCubixx refrigerator: ASD Healthcare will collect de-identified data entered into the MyCubixx touchscreen and information tracked in the myCubixx system. The myCubixx Data is owned exclusively by ASD Healthcare. During the duration of the study, ASD Healthcare will provide the Study Coordinating Center with access to a web portal that contains portions of the myCubixx Data solely for the research team's use in connection with the study.

The sponsor, monitors, auditors, and the IRB will be granted direct access to your research records to conduct and oversee the study. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If we access protected health information (e.g., your medical record), you will be asked to sign a separate form to give your permission. Your medical records may become part of the research record. If that happens, your research records may be looked at by the sponsor of this study and government agencies or other groups associated with the study. They may not copy or take your personal health information from your medical records unless permitted or required by law.

Federal law provides additional protections of your medical records and related health information. These are described in the UC Davis Health System Notice of Privacy Practices (http://www.ucdmc.ucdavis.edu/compliance/pdf/notice.pdf) and in an attached document.

Can I be removed from the research without my OK?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include

☐ You do not follow the study doctor's instructions.

☐ You experience a harmful or high-risk medical condition.

☐ You experience harmful side effects.

☐ Your condition has worsened.

☐ You decide to withdraw from the study.

☐ You require different medicines not allowed on this study.

☐ You are unable to take part and complete study requirements.

☐ The Sponsor or other officials find it necessary to limit or stop this study.

What else do I need to know?

This research is being funded by the Octapharma, also called the grantor. The University of California, Davis School of Medicine, also called the sponsor, is responsible for the design and coordination of this research. Sponsors may change or be added.

UC Davis is being paid to conduct this study. Octapharma USA, Inc. has paid Dr. Ducore and Dr. Thornburg, the principal investigators, for the design and conduct of this study. Dr. Ducore has a

financial interest in Octapharma, the company paying for this study. The sponsor pays Dr. Ducore for travel expenses and professional services, such as speaking engagements and consulting. The income that Dr. Ducore receives is in addition to his salary from the University of California. If you have any questions, please tell the study coordinators and they will put you in touch with someone to talk to.

You or your health plan will be billed for the costs of routine medical care you receive during the study. These costs may include operating room fees, pharmacy charges, treatments, hospitalization, scans, etc. You will be expected to pay for the usual deductibles and co-payments, and for any routine care that is not covered. Only the costs of research or experimental procedures will be paid by the study**.** These procedures are the blood draws and laboratory tests for the study.

For more information about possible costs, please contact the research team. The research team can follow UC Davis Uninsured Non-Emergency Estimate Policy (Policy ID 1883) to work with their department and Decision Support Services to get you a cost estimate.

It is important that you promptly tell the person in charge of the research if you believe that you have been injured because of taking part in this study. If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to your insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about compensation, you may call the IRB Administration at (916) 703-9151 or email at HS-IRBAdmin@ucdavis.edu.

You will not be compensated for taking part in this study.

If you receive the myCubixx refrigerator: In the event your myCubixx device for any reason becomes disabled, or you have any issues with the myCubixx device, the research team will provide you with initial service support to resolve such issues. If the research team is not able to resolve an issue, the research team will notify the Study Coordinating Center at the University of California, Davis. The Study Coordinating Center will advise ASD Healthcare of the issue, stating the nature of the issue and any known cause, all in a manner that ASD Healthcare will not receive your name, address or other identifying information. If deemed appropriate by ASD Healthcare, they will arrange, through its third party affiliate, for the replacement of the myCubixx device.You will not be responsible for any shipping costs associated with the replacement if a myCubixx device.

Your Personal Health Information (PHI) will be provided to a ASD Healthcare third party affiliate for the delivery of a myCubixx device to your house. Your PHI that will be provided to the third party company may include, but is not limited to: your name, address, and telephone number. The third party affiliate has agreed that they will not release this indentifiable information. The research team will not provide ASD Healthcare with your name, address, or other identifiable information, in connection with delivery and return of myCubixx devices.

Signature Block for Capable Adult

Your signature documents your permission to take part in this research.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

Signature of witness to consent process	Date
Printed name of person witnessing consent process	
Printed name of person witnessing consent process	Date

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Signature Block for Children

Your signature documents your permission for the named child to take part in this research.

Printed name of child

Signature of parent or individual legally authorized to consent to the child's general medical care

Date

- ❑ Parent
- ❑ Individual legally authorized to consent to the child's general medical care (See note below)

Printed name of parent or individual legally authorized to consent to the child's general medical care

Note: Investigators are to ensure that individuals who are not parents can demonstrate their legal authority to consent to the child's general medical care. Contact legal counsel if any questions arise.

Signature of parent

Date

Printed name of parent

If signature of second parent not obtained, indicate why: (select one)

- ❑ The IRB determined that the permission of one parent is sufficient.
- ❑ Second parent is deceased
- ❑ Second parent is unknown
- ❑ Second parent is incompetent
- ❑ Second parent is not reasonably available
- ❑ Only one parent has legal responsibility for the care and custody of the child

Assent

- ❑ Obtained
- ❑ Not obtained because the capability of the child is so limited that the child cannot reasonably be consulted.
- ❑ Waived by the IRB because the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the research.

Signature of person obtaining consent and assent

Date

Printed name of person obtaining consent

For IRB stamp and version date only

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